

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE**

CELLECTIS S.A.,

Plaintiff,

v.

PRECISION BIOSCIENCES, INC.,

Defendant.

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) C.A. No. 11-173-SLR-MPT
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CELLECTIS'S OPENING BRIEF ON CLAIM CONSTRUCTION ISSUES

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I. INTRODUCTION

A. Nature & Stage of Proceedings

Pursuant to the Court's "Stipulation and Order to Amend Scheduling Order D.I. 33 & 82" (D.I. 142), Collectis respectfully submits this opening brief with points and authorities in support of its proposed constructions for the disputed terms or phrases appearing in U.S. Patent No. 7,897,372 ("the '372 patent"). Collectis brought this suit against Precision BioSciences, Inc. ("Precision") on March 1, 2011. Discovery has proceeded apace. Fact discovery is set to close on August 31, 2012, and the trial in this matter is scheduled to begin on February 25, 2013.

Meganucleases are proteins that can be found in nature in many single-celled organisms. These meganucleases are highly specific "DNA scissors" that are able to recognize their specific binding site (of, *e.g.*, from 12 to over 30 base pairs in a genome) within an organism in which they reside and cleave (or break) the DNA at or near that binding site. "I-CreI" meganucleases are one member of the family of Group I intron-encoded homing endonucleases, which family was classified by scientists years ago when such homing endonucleases were first identified in nature. I-CreI has been found to be useful in genetic engineering applications and can be engineered to recognize specific DNA cleavage sites in the genome of an organism other than that in which is found in nature.

Plaintiff Collectis was founded in 1999 and is a pioneering company in the field of genetic engineering, particularly with regard to the use of meganucleases as innovative tools to enable targeted modifications in DNA. Collectis's scientists have worked with meganucleases found in nature and have developed techniques to design and make engineered meganucleases. For example, Collectis designs and markets engineered I-CreI meganuclease variants that are

“tailor-made” to cleave a specific site in a given genome of an organism, thereby enabling modification of the genome at that specific targeted cleavage site.

Collectis’s ground-breaking, engineered I-CreI meganuclease variants are useful in numerous fields, such as therapeutics (*e.g.*, gene therapy and antiviral therapy), agricultural biotechnology (*e.g.*, addition or removal of a trait and protein production) and for use in the generation of transgenic organisms. The claims of the ’372 patent define such engineered or tailor-made I-CreI meganuclease variants (which can be used for genetic engineering) and/or monomers that comprise such meganucleases. Meganucleases that fall within the scope of the claims of the ’372 patent have been researched for use in the treatment of xeroderma pigmentosum, a monogenic disease characterized by hypersensitivity to ultraviolet light. Claimed meganucleases have also been designed to target HIV, and genetic disorders including Fanconi anemia and Severe Combined Immune Deficiency (SCID).

In contrast to the extensive research carried out by Collectis, in 2005 Precision essentially copied Collectis’s patented technology to start its own company in 2006. That copying resulted in this lawsuit for infringement of Collectis’s ’372 patent.

B. Summary of Argument

None of the terms in the claims of the ’372 patent should require “interpretation” in the classic sense. They are readily understandable from their plain language to one of ordinary skill in the art and, therefore, should be accorded their ordinary and accustomed meanings to such a person. Those ordinary meanings are supported by the specification and prosecution history of the ’372 patent, as well. If interpretation is needed, Collectis’s proposed meanings of disputed terms presented in the Joint Claim Construction Chart (D.I. 163, the “Joint Chart”) comport with the claim’s plain language and the ’372 patent’s specification. They should be adopted.

Collectis's expert, Dr. David Edgell, agrees, as set forth in his declaration (separately filed on the docket).¹

Precision seeks claim "constructions" that are at odds with the intrinsic evidence, improperly import limitations from the specification, and/or are contrary to the ordinary meanings of the identified terms to a person of ordinary skill in the art. Indeed, in an apparent effort to weave an after-the-fact non-infringement position, Precision attempts to replace the intrinsic evidence with its own, unsupported opinions about what it believes the disputed claim terms should mean.

II. BACKGROUND – STATEMENT OF FACTS

Collectis's '372 patent was issued by the United States Patent and Trademark Office ("the PTO") on March 1, 2011, and it is entitled "I-CreI Meganuclease relates to methods of preparing I-CreI meganuclease variants having a modified DNA cleavage specificity and the I-CreI meganuclease variants themselves that are obtained through such methods. (*See* Edgell Decl., Ex. 1 (the '372 patent) at, *e.g.*, col.1, ll.13-16.) The '372 patent also concerns using these meganuclease variants for cleaving DNA targets or for genetic engineering applications. (Edgell Decl., Ex. 1 at, *e.g.*, col.1, ll.16-19.) Finally, the '372 patent also relates to nucleic acids encoding such meganuclease variants, expression cassettes comprising those nucleic acids, vectors comprising such expression cassettes, and to cells, organisms, plants or animals (except humans) transformed by said vectors. (Edgell Decl., Ex. 1 at, *e.g.*, col.1, ll.20-24.)

Wild-type I-CreI is a homodimer that contains two monomers that are non-covalently associated with one another. Each monomer has 163 amino acids, which are defined in the '372

¹ As of the filing date of this brief, each of claims 1-54 of the '372 patent claims remains at issue and all are addressed through Dr. Edgell's declaration. Discovery is still proceeding and this list may be altered subsequently.

patent as SwissProt accession number P05725 or pdb accession code 1g9y. The '372 patent describes methods for preparing I-CreI meganuclease variants that have amino acid mutations (such as substitutions) at least at certain specified positions relative to the sequence of wild-type I-CreI. For example, the claims of the '372 patent recite a monomer of an I-CreI meganuclease variant, where the monomer comprises at least one mutation, including at least one substitution at one or more of amino acid positions 44, 68 and/or 70, and the monomer also has at least one additional mutation at one or more of amino acid positions 26, 28, 30, 32, 33 and/or 38 (where with the foregoing numbered positions are determined by counting the amino acids relative to the wild-type I-CreI sequence). Such substitutions can involve substituting one amino acid for the amino acid found at that numbered position in wild-type I-CreI. I-CreI meganuclease variants of the '372 patent have the ability to cleave a DNA target site that is not able to be cleaved, for example, by wild-type I-CreI under the same conditions. This change in the meganuclease variant is referred to as "modified DNA cleavage specificity," which is a defined term in the '372 patent. For example, the '372 patent states that "[t]he term 'modified specificity' relates to a meganuclease variant able to cleave a homing site that is not cleaved, in the same conditions by the initial meganuclease (scaffold protein) it is derived from; said initial or scaffold protein may be the wild-type meganuclease or a mutant thereof." (Edgell Decl., Ex. 1 at col.6, ll.45-50; *see* Edgell Decl. at ¶ 15.)

Thus, under the '372 patent, if the scaffold protein is wild-type I-CreI, a variant I-CreI meganuclease has modified DNA cleavage specificity if the wild-type I-CreI does not have the ability to cleave the same target site that the I-CreI meganuclease variant has the ability to cleave, under the same conditions. The '372 patent also describes that an I-CreI meganuclease variant can itself be used as a scaffold protein for inducing further mutations and preparing a

further I-CreI meganuclease variant. (Edgell Decl., Ex. 1 at, *e.g.*, col.11, ll.3-10.) In that case, the further I-CreI meganuclease variant has “modified DNA cleavage specificity” if the first scaffold variant does not have the ability to cleave the same target site that the further variant has the ability to cleave or if wild-type I-CreI does not have the ability to cleave that same target site (“said initial or scaffold protein may be the wild-type meganuclease or a mutant thereof”), again under the same conditions. (*See* Edgell Decl., Ex. 1 at col.6, ll.45-50; *id.* at ¶ 16.)

As further explained in the '372 patent, mutations (such as substitutions) to wild-type I-CreI (or another meganuclease variant scaffold) result in an I-CreI meganuclease variant able to cleave a target site that also is modified (relative, for example, to the target site of wild-type I-CreI) in at least one nucleotide in positions +/- 3 to 5, which are GTC at positions -5 to -3 and GAC at position +3 to +5 in the wild-type. (*See, e.g.*, Edgell Decl., Ex. 1 at col.6, ll.45-50, col. 7, ll.26-30; *id.* at Figure 2.) Such an I-CreI meganuclease variant would have the ability to cleave a target site with at least one nucleotide changed in these +/- 3 to 5 positions, where that target site is not capable of being cleaved by wild-type I-CreI or another I-CreI meganuclease variant used as a scaffold, also under the same conditions. (*See* Edgell Decl. at ¶ 17, Figures 2 & 3.)

The '372 patent is directed to I-CreI meganuclease variants that are homodimers, heterodimers and/or single-chains. A homodimer I-CreI meganuclease variant of the '372 patent can be depicted as A•A, where each A is an identical, mutated monomer, and the “•” represents the non-covalent bonding or association of those two monomers. Under the '372 patent, such I-CreI meganuclease variants also can be prepared as a heterodimer, where each of the two monomers have different amino acid sequences (relative to one another) and at least one such monomer (or domain) in the heterodimer will contain mutations, including at least the specified

substitutions. Such a heterodimer I-CreI meganuclease variant can be depicted as A•B, with each of the A and B monomers having a different amino acid sequence from the other and the “•” representing the non-covalent bonding or association of those two different monomers. (*See* Edgell Decl. at ¶¶ 18-19.)

Further, it is also possible to prepare an I-CreI meganuclease variant known as a single-chain meganuclease in line with the teachings of the '372 patent. In a single-chain, “A” and “B” monomers like those described above are covalently bonded to one another using a linker (amino acid) sequence, which provides a single protein having two monomers (for example, A and A, A and B, B and A, or B and B) associated with one another through that linker. Such single-chain I-CreI meganuclease variants can be depicted, for example, as A∩A, A∩B, B∩A and/or B∩B, where each of the A and B monomers has a different amino acid sequence from the other and the “∩” represents the association or covalent bonding (through a linker) of the two monomers. In the example of an A∩B single-chain I-CreI meganuclease variant, at least one of the monomers (or domains) in the single-chain will have mutations, including at least the specified substitutions. (*See* Edgell Decl. at ¶ 20.)

For example, in light of the above clear language of the '372 patent's claims and specification, claim 37 of the '372 patent recites a “recombinant monomer of an I-CreI meganuclease variant” comprising at least one mutation, including at least one substitution at one or more of amino acid positions 44, 68 and/or 70, and the monomer has at least one additional mutation at one or more of amino acid positions 26, 28, 30, 32, 33 and/or 38 (with the foregoing positions measured by counting the amino acids relative to the wild-type I-CreI sequence), and further states that the “monomer when in dimeric form is able to cleave DNA.” (Edgell Decl., Ex. 1 at col.68, ll.37-48.) Especially in view of the parties' agreement that the phrase “when in

dimeric form” means “when two monomers are associated,” the recited “recombinant monomer” of claim 37 quite clearly can be non-covalently associated with another monomer (such as an A•A homodimer or A•B heterodimer I-CreI meganuclease variant) or covalently associated through a linker with another monomer (for example, as in an A∩B single-chain I-CreI meganuclease variant). (See Edgell Decl. at ¶ 21, Figures 2 & 3.)

III. ARGUMENT

A. THE LAW OF CLAIM CONSTRUCTION

Claim construction is a question of law reserved exclusively for the court. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 970-71 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996). A court is required to give each disputed claim term the meaning it would have had to “one of ordinary skill in the art at the time of the invention.” *Id.* at 986. Thus, the court must view the claims through the lens of a person of ordinary skill in the art when construing the claim terms. See *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (en banc). A person of ordinary skill in the art is expected to read the claim both in “the context . . . in which the disputed term appears,” and also in the context of the patent in its entirety. *Id.* at 415 F.3d at 1313. Claim construction, therefore, should focus first and foremost on the claim language itself, and claim terms “are generally given their ordinary and customary meaning.” *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996).

While claim terms should be construed in light of the patent specification, it is legal error to import into the claim limitations from the specification. *Phillips*, 415 F.3d at 1323. There is a difference between construing a term appearing in a claim, and adding a limitation that is not there in the first place. *Id.* The former is permissible; the latter is not. *Id.* “Courts can neither broaden nor narrow the claims to give the patentee something different than what he has set

forth.” See *E.I. Du Pont de Nemours & Co. v. Phillips Petroleum Co.*, 849 F.2d 1430, 1433 (Fed. Cir. 1988) (quoting *Autogiro Co. of America v. United States*, 384 F.2d 291 (Ct. Cl. 1967)). Moreover, it is not necessary to construe every claim. E.g., *Silicon Graphics, Inc. v. ATI Techs., Inc.*, 607 F.3d 784, 798 (Fed. Cir. 2010) (affirming district court’s choice to apply claim term’s ordinary meaning rather than construing the same); see also *Finjan, Inc. v. Secure Computing Corp.*, 626 F.3d 1197, 1207 (Fed. Cir. 2010) (holding that the district court did not err by rejecting defendants’ construction and instructing jury to give the claim term its “ordinary meaning”); *U.S. Surgical Corp. v. Ethicon, Inc.*, 103 F.3d 1554, 1568 (Fed. Cir. 1997) (claim construction “is not an obligatory exercise in redundancy”).

Collectively, the patent and its prosecution history comprise the so-called “intrinsic evidence,” which constitutes the public record with respect to a patent, and people must be able to rely on that record to determine the meaning of a claim term. Accordingly, courts must rely, to the extent possible, on the intrinsic evidence to determine the meaning of claim terms. *Phillips*, 415 F.3d at 1317; *Kara Tech. Inc. v. Stamps.com Inc.*, 582 F.3d 1341, 1348 (Fed. Cir. 2009). Although a patentee may use the specification to assign unique definitions to claim terms, limitations from the written description should generally not be imported into the claims. *Phillips*, 415 F.3d at 1315–16, 1320, 1323. In particular, the description of an embodiment in the specification does not, without more, limit the claims to that single embodiment. *Id.* at 1323 (“we have expressly rejected the contention that if a patent describes only a single embodiment, the claims of the patent must be construed as being limited to that embodiment”). A patent’s prosecution history can also be considered. *Id.* at 1317 (“Like the specification, the prosecution history provides evidence of how the PTO and the inventor understood the patent.”). However,

the prosecution history “often lacks the clarity of the specification and thus is less useful for claim construction purposes.” *Id.*

If a claim term’s meaning cannot be determined from the intrinsic evidence, a court also may consider certain forms of extrinsic evidence to aid in determining the “true meaning of language employed” in the claims. *Markman*, 52 F.3d at 980-81 (citations omitted). However, improper reliance on extrinsic evidence in the form of experts must not be used to vary or contradict the intrinsic evidence. *Phillips*, 415 F.3d at 1318 (“conclusory, unsupported assertions by experts as to the definition of a claim term are not useful to a court. Similarly, a court should discount any expert testimony ‘that is clearly at odds with the claim construction mandated by the claims themselves, the written description, and the prosecution history, in other words, with the written record of the patent.’” (quoting *Key Pharms. v. Hercon Lab. Corp.*, 161 F.3d 709, 716 (Fed. Cir. 1998))).

B. Collectis’s Construction of the Disputed Terms Should Be Adopted

The claims of the ’372 patent are readily understandable to a person of ordinary skill in the art from their plain language, and should be given their ordinary meanings to such a person. Those ordinary meanings are fully supported by the specification and prosecution history of the ’372 patent. (*See* Ex. A attached hereto (the ’372 prosecution history).) There is nothing in the intrinsic evidence to contradict those ordinary meanings; to the contrary, the intrinsic evidence fully supports them. If interpretation is needed, Collectis’s proposed claim meanings of disputed terms in the Joint Chart should be adopted because they comport with the ordinary meanings of those claims and the ’372 patent’s specification. In that regard, while the below discussion presents the disputed claim terms separately from the claim language as a whole in which those terms appear, Collectis’s below proposals account for the meanings of each of these terms in the

context of the entire claim (or claims) in which those terms appear, as well as in the context of the '372 patent's specification and prosecution history.

To the extent the Court desires expert guidance, Dr. David Edgell provides a declaration supporting Collectis's proffered claim meanings, in which he states his agreement that the '372 patent specification supports the ordinary meanings ascribed to the disputed claim terms in Collectis's proposals.² Finally, with regard to all claim terms not in dispute (and, therefore, not addressed below), Collectis contends that those terms should be ascribed their ordinary accustomed meanings to a person of ordinary skill in the art. Dr. Edgell agrees. (*See* Edgell Decl. at ¶ 26.)

C. The Claim Language and Specification Supports Collectis's Constructions

Disputed Claim Term	Proper Construction
monomer of an I-CreI meganuclease variant	a polypeptide from an I-CreI meganuclease variant

The claim term "monomer of an I-CreI meganuclease variant" is recited in claims 1-5, 19-23, and 37-41 of the '372 patent, and is also included in dependent claims 6-18, 24-36, and 42-54, each of which references one of the foregoing claims. There is no dispute that a "monomer" is a well-known term in the field of the '372 patent and would be understood by a

² Dr. Edgell provides a definition of a person of ordinary skill in the art to which the '372 patent pertains, and his opinions on the meanings of claim terms are offered from the viewpoint of such a person on March 15, 2005. (*See* Edgell Decl. at ¶ 10) Reference in this brief to one of ordinary skill in the art is made with that definition and time-frame in mind. As noted in Dr. Edgell's declaration, the claims of the '372 patent are subject to an ongoing reexamination in the PTO, and amendments have been proposed during that reexamination. For example, claims 4, 22 and 40 have been cancelled and their elements (relating to "modified DNA cleavage specificity . . .") have been incorporated into the claims from which they respectively depend, namely claims 1, 19 and 37. However, if these amendments are entered and the claims issued accordingly, that would not change the Collectis's positions on the meanings of claim terms discussed in the brief. Dr. Edgell agrees. (*See id.* at ¶ 28.)

person of ordinary skill in the art to have the ordinary meaning on which the parties agreed in the Joint Chart, namely “a molecular building block – *e.g.*, a polypeptide – that can be associated with another to form a larger molecule.” Moreover, the word “monomer” in the above claim term is written singular in tense, thereby clearly signifying only one monomer (or polypeptide), just as Collectis proposes.

In an apparent effort to develop a non-infringement argument, Precision wrongly suggests that monomer should be construed as referring to “one of two polypeptides,” that “can act together to form an I-CreI variant homodimer.” Precision’s argument is contradicted by the plain claim language (which states a monomer, *not* two monomers) and because the claims containing the above term are not narrowly limited to homodimers. For example, in claim 37 of the ’372 patent (which contains the phrase “recombinant monomer of an I-CreI meganuclease variant”), the claimed recombinant monomer can be part of a homodimer, heterodimer or single-chain I-CreI meganuclease variant. *See above*. Moreover, the specification of the ’372 patent describes both heterodimers (Edgell Decl., Ex. 1 at col.6, ll.61-66) and single-chain meganucleases (Edgell Decl., Ex. 1 at, *e.g.*, col.10, ll.25-34.). Thus, there is simply no basis for Precision’s attempt to read those disclosures out of the above claim term and the claims incorporating that term. For all these reasons, particularly the plain and ordinary meaning of this claim term, and the parties agreement on the definition of a “monomer,” Collectis’s above, proposed construction should be adopted, and Precision’s contrary proposal should be rejected. Dr. Edgell agrees. (*See* Edgell Decl. at ¶¶ 29-30.)

Disputed Claim Term	Proper Construction
monomer of an I-CreI meganuclease variant comprising at least one mutation in the amino acid sequence of SEQ ID NO: 70, wherein said at least one mutation comprises a substitution	monomer of an I-CreI meganuclease variant comprising at least one mutation in the amino acid sequence of SEQ ID NO: 70, wherein said at least one mutation comprises a substitution

<p>at one or more of the amino acids residues at positions 44, 68 and 70 and said monomer further comprises at least one additional mutation of an amino acid residue directly contacting a DNA target sequence wherein said amino acid residue directly contacting a DNA target sequence is selected from the group consisting of positions 26, 28, 30, 32, 33 and 38</p>	<p>at one or more of the amino acid residues at positions 44, 68 and 70 with reference to the amino acid numbering of SwissProt accession number P05725 or pdb accession code 1g9y and said monomer further comprises at least one additional mutation of an amino acid residue at positions 26, 28, 30, 32, 33 or 38 with reference to the amino acid numbering of SwissProt accession number P05725 or pdb accession code 1g9y</p>
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Independent claims 1, 19 and 37 of the '372 patent each include the above term that identifies amino acid residues for mutations and/or substitutions at various numbered positions. Each of dependent claims 2-18, 20-36, and 38-54 depends from one of claims 1, 19 or 37 and, therefore, also includes the above claim term. Cellectis's proposed construction is taken straight from the patent specification, which makes it abundantly clear that the numbering of such amino acid residues must be done with reference to the amino acid numbering of SwissProt accession number P05725 or pdb accession code 1g9y, which are the wild-type I-CreI. (Edgell Decl., Ex. 1 at, *e.g.*, col.5, ll.43-47.) On that basis alone, Cellectis's proposed construction with regard to amino acid numbering should be adopted. A person of ordinary skill in the art would understand this numbering system from clear language describing it in the '372 patent's specification and would apply that convention to the amino acid positions to be mutated or substituted on SEQ ID NO. 70 (which is recited in the above claim term, and has an extra alanine, "Ala" or "A", at position 2). Because SEQ ID NO. 70 has that extra alanine that is not present in wild-type I-CreI, in light of the '372 patent's specification, a person of ordinary skill in the art would disregard that alanine in counting the amino acid sequence of SEQ ID NO. 70 and determining mutation positions relative to the amino acid positions specified in the above claim term.

Moreover, the above claim term uses the open-ended language “comprising” (*e.g.*, “comprising at least one mutation in the amino acid sequence of SEQ ID NO: 70”), which means that the recited SEQ ID NO. 70 monomer can have further mutations, in addition to those substitutions and mutations that are specifically identified by numbered position in the claims. Indeed, the broadest transition phrase in patent claim drafting is “comprising,” which is considered open-ended in that it “does not exclude additional unrecited elements.” *Molecular Research Corp. v. CBS, Inc.*, 793 F.2d 1261, 1271 (Fed. Cir. 1986); “M.P.E.P.” § 2111.03. (*See* Ex. B attached hereto (M.P.E.P. § 2111.03).) Precision’s proposed construction of the above claim term eliminates “comprising” from the claim, and therefore improperly results in a much narrower construction, more akin to “consisting of” language, which excludes more than traces of ingredients (or, here, substitutions) other than those expressly listed. M.P.E.P. § 2111.03 (*see* Ex. B); *Ex parte Grasselli*, No. 544-99, 231 U.S.P.Q. 395, 395 (B.P.A.I. Sept. 27, 1983). There is no basis for Precision’s attempt to read “comprising” out of the above claim term. It is a transparent attempt to narrow the claims in the hope of creating a non-infringement position where none properly exists.

Collectis’s proposed construction should be adopted. It tracks the plain language of the claims, includes the amino acid numbering convention expressly described in the specification, and gives the word “comprising” its recognized scope in the patent law. Dr. Edgell agrees that a person of ordinary skill in the art would understand the above term as Collectis advocates. (*See* Edgell Decl. at ¶¶ 31-32.)

Disputed Claim Term	Proper Construction
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modified DNA cleavage specificity relative to the I-CreI meganuclease of SEQ ID NO: 70 in at least one nucleotide in the +/- 3 to 5 triplets	having the ability to cleave a DNA target site that has at least one nucleotide mutation in the gtc triplet at positions -5 to -3 or the gac triplet at positions +3 to +5, where the DNA target site is not cleaved in the same conditions by an initial meganuclease scaffold
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The above claim term is recited in claims 4, 22 and 40 and relates to the modified DNA cleavage specificity of the I-CreI meganuclease variant containing the recited monomer in the claims (1, 19 and 37, respectively) from which they depend. There is no legitimate question about the meaning of such “modified DNA cleavage specificity” given its plain language, and because the ’372 patent expressly states that “[t]he term ‘modified specificity’ relates to a meganuclease variant able to cleave a homing site that is not cleaved in the same conditions by the initial meganuclease (scaffold protein) it is derived from; said initial or scaffold protein may be the wild-type meganuclease or a mutant thereof.” (Edgell Decl., Ex. 1 at col.6, ll.45-50.) Further, the ’372 patent expressly states that an I-CreI meganuclease variant can itself be used as a scaffold meganuclease for inducing additional mutations and preparing a further I-CreI meganuclease variant. (Edgell Decl., Ex. 1 at, *e.g.*, col.11, ll.3-10.) Thus, according to the plain language of the claims, and in light of the foregoing guidance from the specification, an I-CreI meganuclease variant having the recited “modified DNA cleavage specificity” in the above claim term would have the ability to cleave a target site with at least one nucleotide change in the recited +/- 3 to 5 positions (which are known to be gtc for -5 to -3 and gac for +3 to +5 for wild-type I-CreI), which target site is not capable of being cleaved by wild-type I-CreI (or another I-CreI meganuclease variant used as a scaffold), under the same conditions.

Accordingly, a person of ordinary skill in the art would understand from the ’372 patent in that “modified DNA cleavage specificity” is determined by whether the initial meganuclease,

a scaffold I-CreI meganuclease variant or wild-type I-CreI, has the ability to cleave the same target site (with at least one nucleotide changed in the above-specified +/- 3 to 5 positions) that the claimed I-CreI meganuclease variant has the ability to cleave (with the claimed variant having such “modified DNA cleavage specificity” if the scaffold variant or wild-type I-CreI does not cleave that target site; *see* Edgell Decl., Ex. 1, at *id.*; *see also* Edgell Decl. at Figure 4). For all of these reasons, particularly the plain language of the claims and the specification’s clear guidance, Collectis’s construction should be adopted. Dr. Edgell agrees with this construction. (See Edgell Decl. at ¶¶ 33-34.)

In sharp contrast to the above claim construction logic, Precision engages in wholesale importation of part of the specification of the ’372 patent into the above claim term. There is no basis in the ’372 patent, much less a reference in the claim, for making such an improper importation of limitations. Indeed, Precision effectively rewrites the entire claim term to include a formula that pertains to only half of even the specified mutations or substitutions in the claims. Precision’s proposal is divorced from the reality of the plain claim language and the express guidance of the specification of the ’372 patent. It should be rejected on that basis alone.

Disputed Claim Term	Proper Construction
A44/A68/A70 . . . T44/S68/K70 (abbreviated for convenience – please see full ’372 patent for entire term)	The nomenclature “X”44/“Y”68/“Z”70 means a variant monomer having amino acid residues, “X,” “Y” and “Z” at position 44, 68 and 70 with reference to the amino acid numbering of SwissProt accession number P05725 or pdb accession code 1g9y

The term “A44/A68/A70 . . . T44/S68/K70” relates to a list of groups of specific amino acid substitutions at the identified, numbered positions. This term is found in dependent claims 5, 23 and 41 of the ’372 patent. Collectis’s proposed construction for this term is supported by the plain language of the claims and is completely consistent with the specification of the ’372

patent. (*See, e.g.*, Edgell Decl., Ex. 1 at col.5, ll.43-46, and col.7, l.51 to col.8, l.62.) As discussed above, with reference to the passage at column 5, lines 43-46, the '372 patent is quite clear and exact with regard to the numbering of amino acid positions for mutation and/or substitution in the claimed monomers of an I-CreI meganuclease variant. A person of ordinary skill in the art would understand from reading the specification that all such amino acid positions are numbered with reference to SwissProt accession number P05725 or pdb accession code 1g9y, the wild-type I-CreI. Collectis's proposed construction should be adopted. Dr. Edgell agrees. (*See* Edgell Decl. at ¶ 35-36.)

Disputed Claim Term	Proper Construction
single-chain chimeric meganuclease comprising [a] fusion of [two monomers]	a meganuclease in the form of a single protein comprising a first monomer fused to a second monomer

The claim term “single-chain chimeric meganuclease comprising [a] fusion of [two monomers]” appears in claims 13-18, 31-36, and 49-54 of the '372 Patent. This term should be construed in light of the specification, which expressly teaches that I-CreI meganucleases are proteins. (*See, e.g.*, Edgell Decl., Ex. 1 at col.3, ll.17-22; col.11, ll.11-17; col.17, ll.11, 27-35; col.17, l.66 to col.18, l.20; col.22, ll.17-30; col.24, ll.18-23; col.27, ll.20-33; and col.28, ll.23-25, 34-38.) Therefore, on that basis alone, a person of ordinary skill in the art would understand from the plain language of this term (and the specification) that it means “a meganuclease in the form of a single protein comprising a first monomer fused to a second monomer,” as Collectis proposes.

Precision wrongly asserts that this claim term should be limited to a “single polypeptide.” It is well-known that a protein has a function (just as a meganuclease does, which is a central word in the above claim term), as compared to a polypeptide which may not necessarily have a

function. Moreover, Precision's proposal is contradicted by its agreement in the Joint Chart that a "monomer" should be defined as "a polypeptide." *See above*. A meganuclease is indisputably comprised of more than one monomer (or polypeptide), *see above*, so Precision's proposal that the above claim term should be "construed" to mean a "single polypeptide" makes no sense and is not compliant with its prior agreement about the meaning of "monomer." These are additional reasons why Collectis's proposal should be adopted and Precision's rejected. Dr. Edgell agrees. (*See Edgell Decl. at ¶¶ 37-38.*)

Disputed Claim Term	Proper Construction
wild-type monomer from I-DmoI	a naturally occurring amino acid sequence from I-DmoI that has the ability to cleave DNA when in dimeric form with a monomer of I-CreI

The term "wild-type monomer from I-DmoI" is found in claims 7, 11-13, 17-18, 25, 29-31, 35-36, 43, 47-49, 53-54. A person of ordinary skill in the art would know that, in the wild, I-DmoI exists as a single-chain endonuclease, which has two domains or monomers, just as wild-type I-CreI has two monomers (which non-covalently associate to form a homodimer). Thus, the plain language of the term "wild-type monomer from I-DmoI" means a naturally occurring amino acid sequence from I-DmoI. There is nothing in the claim term or the '372 patent's specification that warrants, much less requires, that it is limited to the entire sequence of the I-DmoI protein as found in the wild, which is the position wrongly advocated by Precision. Rather, it is apparent from the plain language that any naturally occurring amino acid sequence from either domain (or monomer) of I-DmoI, having the ability to cleave DNA when in dimeric form with a monomer of I-CreI, is included in this claim term.

Indeed, Precision's proposal for limiting this term to the entire amino acid sequence of PDB accession number 1b24 is misguided, not supported by the '372 patent in any respect and

contrary to law. Unless a patent specification or subsequent prosecution history limits the broadest construction of a term, it is improper to construe a term in such a way that would read in limitations. *See Superguide Corp. v. DirecTV Enters., Inc.*, 358 F.3d 870, 875 (Fed. Cir. 2004) (“[I]t is important not to import into a claim limitations that are not a part of the claim.”). The amino acid sequence PDB 1b24 (which constitutes the amino acid sequence for the entire wild-type I-DmoI, not just a part thereof) does not appear anywhere in the ’372 patent. Moreover, Precision’s proposal once again contradicts its agreed upon definition of “monomer” (which appears in the above term in the singular tense) because it would turn a single “monomer” (or polypeptide) into an entire single-chain protein (comprised of two monomers or domains or polypeptides) and improperly limit it to that same definition. Dr. Edgell agrees. (*See* Edgell Decl. at ¶¶ 39-40.)

Disputed Claim Term	Proper Construction
variant of the wild-type monomer from I-CreI	a mutant monomer of I-CreI, which when in dimeric form, retains the ability to cleave DNA
variant of the wild-type monomer from I-DmoI	a mutant monomer of I-DmoI that has the ability to cleave DNA when in dimeric form with a monomer of I-CreI

The term “variant of the wild-type monomer from I-CreI” is found in claims 7, 10, 13, 16, 25, 28, 31, 34, 43, 46, 49, and 52. The term “variant of the wild-type monomer from I-DmoI” is found in claims 7, 12-13, 18, 25, 30-31, 36, 43, 48-49, and 54. The meanings of these two claim terms are clear from the plain language of the claims. Indeed, the words “variant” and “mutant” are rife throughout the ’372 patent, which is chiefly directed to such variant or mutant monomers as part of creating meganuclease variants for use in genetic engineering. That plain language indicates these two claim terms should be given their above, ordinary meanings to a person of skill in the art, which meanings are also supported by the specification of the ’372

patent. (Edgell Decl., Ex. 1 at col.1, ll.13-19, and col.7, ll.45-50). On that basis alone, Collectis's above constructions of these terms should be adopted. Collectis's proposed constructions are further supported because each of the above claims containing this language specify, for example, meganuclease variants that are heterodimers or single-chain meganucleases, which in each instance requires association of two monomers. Therefore, a person of ordinary skill in the art would understand that a "variant of the wild-type monomer from I-CreI" is a mutant monomer of I-CreI that, when in dimeric form, retains the ability to cleave DNA and that a "variant of the wild-type monomer from I-DmoI" is a mutant monomer of I-DmoI that has the ability to cleave DNA when in dimeric form with a monomer of I-CreI. Dr. Edgell agrees with Collectis's proposed constructions. (See Edgell Decl. at ¶¶ 41-42.)

Precision does not even proffer a proposed construction for these terms, but instead flatly avers in the Joint Chart that each of them is "indefinite" under 35 U.S.C. § 112, ¶ 2. That argument is not a proper one for claim "construction," as opposed to a patent validity analysis. Nevertheless, it is worth noting that the Federal Circuit has explained that a claim is not indefinite merely because reasonable persons may disagree on its construction. See *Bancorp Servs., L.L.C. v. Hartford Life Ins. Co.*, 359 F.3d 1367, 1371-72, 1376 (Fed. Cir. 2004) (reversing a grant of summary judgment of indefiniteness where the meaning of the term "surrender value protected investment credits" was "reasonably discernible"). Indeed, a claim may be held invalid as indefinite only if it is impossible to understand. *Source Search Techs., LLC v. LendingTree, LLC*, 588 F.3d 1063, 1076 (Fed. Cir. 2009) ("If the meaning of the claim is discernible, even though the task may be formidable and the conclusion may be one over which reasonable persons will disagree, we have held the claim sufficiently clear to avoid invalidity on indefiniteness grounds. Only claims not amenable to construction or insolubly ambiguous are

indefinite.”) (citations and internal quotation marks omitted). Here, these claim terms plainly are not impossible to understand. Further, Precision tellingly has not even bothered to disagree with the foregoing constructions, which are based on the ordinary meanings of these terms in any event and, therefore, would be difficult to legitimately dispute. There is simply no basis for Precision’s indefiniteness argument. It should be rejected and Collectis’s proposed constructions adopted.

IV. CONCLUSION

For the reasons stated above, Collectis’s constructions for each of the disputed claim terms should be adopted, and the remaining claim terms should be given their ordinary meanings.

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CERTIFICATE OF SERVICE

I hereby certify that on August 15, 2012, I electronically filed the foregoing document with the Clerk of the Court using CM/ECF and have also served the parties below as noted:

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